Daily allergic multimorbidity in rhinitis using mobile technology

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Daily allergic multimorbidity in rhinitis using mobile technology: a novel concept of the MASK study

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Short title: Allergic multimorbidity using an App

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Abstract

Background: Multimorbidity in allergic airway diseases is well known, but no data exist about the daily dynamics of symptoms and their impact on work. To better understand this, we aimed to assess the presence and control of daily allergic multimorbidity (asthma, conjunctivitis, rhinitis) and its impact on work productivity using a mobile technology, the *Allergy Diary,*

Methods: We undertook a one year prospective observational study in which 4,210 users and 32,585 days were monitored in 19 countries. Five visual analogue scales (VAS) assessed the daily burden of the disease (i.e. global evaluation, nose, eyes, asthma and work). VAS levels <20/100 were categorized as "Low" burden and VAS levels ≥50/100 as "High" burden.

Results: VAS global measured levels assessing the global control of the allergic disease were significantly associated with allergic multimorbidity. Eight hypothesis-driven patterns were defined based on "Low" and "High" VAS levels. There were <0.2% days of Rhinitis Low and Asthma High or Conjunctivitis High patterns. There were 5.9% days with a Rhinitis High - Asthma Low pattern. There were 1.7% days with a Rhinitis High – Asthma High – Conjunctivitis Low pattern. A novel Rhinitis High - Asthma High - Conjunctivitis High pattern was identified in 2.9% days and had the greatest impact on uncontrolled VAS global measured and impaired work productivity. Work productivity was significantly correlated with VAS global measured levels.

Conclusions: In a novel approach examining daily symptoms with mobile technology we found considerable intra-individual variability of allergic multimorbidity including a previously unrecognized extreme pattern of uncontrolled multimorbidity.

Key words: Asthma, conjunctivitis, multimorbidity, rhinitis, work productivity

Abbreviations

AR: allergic rhinitis

ARIA: Allergic Rhinitis and its Impact on Asthma

ICT: information and communications technology

MACVIA: Contre les MAladies Chroniques pour un VIeillissement Actif

MASK: MACVIA-ARIA Sentinel NetworK

MeDALL: Mechanisms of the Development of Allergy (FP7)

VAS: visual analogue scale

2,834 words

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Introduction

Allergic diseases are complex and often cluster resulting in multimorbidity [1]. It is estimated that the vast majority of patients with asthma have rhinitis. Conversely, around 20-40% of patients with allergic rhinitis (AR) experience bronchial symptoms [1-3] irrespective of the allergic sensitization [4]. There are several unmet needs in the understanding of the relationship between upper and lower airways pathophysiology [2,5,6]. In particular, the stated prevalence of nasal, bronchial and ocular symptoms in AR varies widely between studies. In some clinical trials with patients suffering from moderate to severe asthma, the vast majority of patients also have rhinitis multimorbidity. Eye symptoms have been largely studied in rhinitis and asthma [1-3,7,8] and often represent the most severe AR symptoms [9-11]. However, there is little information concerning the impact of eye symptoms on global disease severity or control, or their association with the asthma-rhinitis multimorbidity. No study has assessed multimorbidity on a daily basis whereas environmental exposure varies widely between days.

Two approaches can be proposed to assess multimorbidity. In MeDALL (Mechanisms of the Development of Allergy, FP7)[12,13], both hypothesis-driven [14] and data-driven approaches with machine learning tools [15,16] were used. However, so far, previous studies have not considered the daily joint co-occurrence of multimorbidity symptoms.

MASK-rhinitis (MACVIA-ARIA Sentinel NetworK for allergic rhinitis) is a patient centred ICT (information and communication technologies) system [17,18]. A mobile phone app (*Allergy Diary)* central to MASK is available in 22 countries. It has been validated [19] and was found to be an easy and effective method of assessing symptoms of AR using a VAS and work productivity [19-23].

In order to better understand daily allergic multimorbid patterns, the *Allergy Diary* was used over a one-year period assessing days instead of patients.

Methods

Design of the study

An observational study was carried out on all users who filled in the *Allergy Diary* from May, 25, 2016 to May 24, 2017. Five visual analogue scales (VAS) assessed the daily control of the disease (i.e. global evaluation of allergic symptoms, nose, eye, asthma and work productivity) [20]. The primary objective of the study was to assess prevalence and control of the daily allergic multimorbidity (asthma, conjunctivitis, rhinitis) according to recorded daily overall control (global evaluation). Secondary objectives included the impact of multimorbidity on work and the characterization of multimorbid patterns. In this study, a hypothesis-driven approach was used to select groups depending on VAS levels (high level: VAS≥50/100, low level: VAS < 20/100) [12].

The paper was written according to the STROBE checklist.

Setting

Users from 19 countries filled in the *Allergy Diary* (Table 1). The three countries with under 25 users were excluded from the analysis (i.e. Canada, Czech Republic and Turkey). The *Allergy Diary* is available in 16 languages (translated and back-translated, culturally adapted and legally compliant).

Users

All consecutive users who registered to the *Allergy Diary* were included if they had filled in the VAS global measured. The first question of the Allergy Diary is “do you have allergic rhinitis (Yes, No)?” There were no exclusion criteria. Some demographic characteristics (age, sex, country and language) were recorded. The *Allergy Diary* was used by people who found it on the internet, Apple store, Google Play or in any other way. Some users were clinic patients who were asked by their physicians to use the app. However, due to anonymization of data, no specific information could be gathered as previously described in detail [21,22].

Allergy Diary and outcomes

The app collects information on AR symptoms experienced on a specific day. Geolocalized users assess their daily symptom control via the touchscreen functionality on their smart phone: they click on 5 consecutive VAS measures (VAS-global measured, VAS-nasal, VAS-ocular, VAS-asthma and VAS-work). Levels range from zero (not at all bothersome) to 100 (very bothersome). Independency of VAS questions was previously assessed using the Bland and Altman regression analysis [22,24].

Some of the VAS data used in this study have been analyzed in other studies with a different aim including work productivity [21] and assessment of treatment (paper in press). Moreover, the time frame of the two other studies was different.

Ethics

The Allergy Diary is CE1 registered. However, it is not considered by the Ethical Committee of the Cologne Hospital or the MHRA (Medicines and Healthcare products Regulatory Agency - GOV.UK) as a medical device as it does not give any recommendations concerning treatment or diagnosis. The terms of use have been translated into all languages and customized according to the legislation of each country. This thereby allows the use of the results for research purposes. The data are anonymized except for the geolocalized data that are never totally anonymous [21,22]. An Independent Review Board approval was not needed for this observational study.

Biases

As for all studies using big data, there are biaises which should be considered. These include sampling bias likely present, difficult to assess generalizability of the study, outcome misclassification cannot be assessed and, by definition due to ethical problems, there very little information on patient (or day) characteristics.

In the database, 1,860 users have filled in the VAS for over a week. Thus, the analysis of days that correspond to repeated observations for the same individuals is likely to have inflated the correlation between the different types of VAS. In a previous study, it was found that the correlation between VAS global measured and VAS nose increased from Rho=0.76 for day 1 to Rho=0.83 for all days[21]. Moreover, this was also confirmed in the validation study [19]

For this study, other biases should be considered. The diagnosis of AR was not supported by a physician but was a response to the question: “Do you have allergic rhinitis? Yes/No”. There may therefore be some users with non-allergic rhinitis who may have responded “Yes” to the question. The

treatments are not considered since there is a need for a combined symptom-medication score that is currently being developed. However, it was found that the level of control of allergic symptoms (asthma or rhinitis) was independent of treatment [25,26] making it possible to analyze the data.

Size of the study

In this exploratory pilot study, all registered users over the one-year study period were included to obtain the best possible estimates for the specified time window.

Statistical analysis

Some of the data did not follow a Gaussian distribution. Medians and percentiles as well as non-parametric tests were used for data following a non-Gaussian distribution. The statistically significant correlations were ascribed to "very strong" (Rho ranging from 0.80 to 1.00), "strong" (Rho ranging from 0.60 to 0.79) or "moderate" (Rho ranging from 0.40 to 0.59) [21]. We then assessed allergic multimorbidity using cutoff values proposed by consensus (0-19, 20-49 and 50/100) [27].

Results

Users

From May 24, 2016 to May 25, 2017, a total of 4,210 users from 19 countries filled in the VAS (Table 1). They ranged in age from 12 to 92 years (mean ± SD: 39 ±16.5 years). There were 2,169 females (51.5%) and 2,041 males (48.5%). 1,860 users filled in the VAS once only, 1,517 from 2 to 7 days, 349 from 8 to 15 days and 484 filled it in for over 16 days (up to 365 days). Less than 10% of users were over 60 years and we did not stratify the study by age.

Overall results

32,585 days were recorded for VAS global measured, nose and eyes, but only 32,095 (98.5%) days for VAS asthma (due to a delay in translations in some of the countries) and 17,505 (53.1%) days for VAS work since only a proportion of users were working.

Median VAS levels all increased similarly with the increasing level of VAS global measured although VAS nose levels are higher than the others (Table 2).

There were 7,052 (21.6%) days with a measurement of zero for VAS global measured and 18,488 for asthma (Tables 1 online). The prevalence of days with VAS ≥1 decreased from VAS nose to VAS work, VAS eye and VAS asthma (Figure 1). Over 80% days with VAS global measurement ≥50 had a detectable VAS eye. On the other hand, up to 62% of days with VAS global measurement ≥50 had a detectable VAS asthma. For days with VAS level ≥ 1, median levels of VAS increased with the global severity of the day and were similar for asthma, eye and work (Figure 1).

Using the Spearman rank correlation for the entire database, we found significant correlations between all VAS levels (Table 1 online, Figure 1 online):

- A very strong correlation was found between VAS global measurement and nose (Rho > 0.88) or work (Rho > 0.82),
- A strong correlation was found between VAS global measurement and eye (Rho > 0.71), VAS nose and eye (Rho > 0.63) or work (Rho > 0.77), VAS eye and work (Rho > 0.69) and VAS asthma and work (Rho > 0.60).
- A moderate correlation was found between VAS asthma and global measurement (Rho > 0.55), nose (Rho > 0.50) and eye (Rho > 0.52).

Patterns of daily multimorbidity of allergic rhinitis

We studied four asthma-nose or eye-nose distinct patterns according to the consensus on VAS control: 0-19 (Low: well controlled), 20-49 (partly controlled) and ≥50 (High: uncontrolled) (Figure 2).

There were very few days (<0.5%) with High Asthma or High Conjunctivitis and Low Rhinitis. There were also few days (<0.5 %) with low asthma or low conjunctivitis and high rhinitis.

The correlation between VAS eye and asthma is moderate (Rho=0.53) (Figure 2 online).

Daily Asthma-Rhinitis patterns were dependent on VAS global measured (Figure 3). The same trends were found for the Conjunctivitis-Rhinitis patterns.

- Asthma Low (<20) - Rhinitis Low (<20): This pattern was mainly found for VAS global measured levels <20 and at a lesser extend for VAS <50.
- Asthma High (≥50) - Rhinitis Low (<20): This pattern was extremely rare (<0.5%) for all VAS global measured levels.

- Asthma Low (<20) - Rhinitis High (≥50): This pattern was extremely rare in VAS global measured levels <20 (< 0.5%), was rare for 20-49 and was frequent for levels ≥50.
- Asthma High (≥50) - Rhinitis High (≥50): This pattern was almost exclusively found in VAS global measured levels ≥50.

There was a very large number of zero values (N=13,915 for VAS eye and N=18,488 for VAS asthma). There are 1.8% days with an Asthma High-Conjunctivitis Low pattern and 5.2% days with Asthma Low-Conjunctivitis High pattern.

The same trends were found for the Conjunctivitis-Rhinitis patterns. Slightly over 14% days had a VAS nose ≥ 50 (Rhinitis High) (Table 3). Among them, four groups were identified: (i) Asthma Low and Conjunctivitis Low, (ii) Asthma Low and Conjunctivitis High, (iii) Asthma High and Conjunctivitis Low and (iv) the extreme pattern: Asthma High and Conjunctivitis High. The levels of VAS global and work increased significantly between the four patterns. In the extreme pattern (Nose, eye and asthma High), there was an increased VAS level of all five criteria. The yearly repartition of uncontrolled rhinitis, conjunctivitis and asthma indicates that there is an over-representation of days in March, April, May and June (Figure 3 online). However, these patterns were observed for all other months.

In order to assess whether reporting VAS levels on day 1 may affect the results, we studied 1,060 users who reported at least one day of rhinitis VAS ≥50 and over two days of VAS: 145 (13.7%) had a VAS ≥50 on day 1 only, 498 (47%) had a VAS ≥50 on day 1 and another day, and 417 (39.3%) had a VAS <50 on day 1 and ≥50 another day.

Discussion

This observational study is, to our knowledge, the first to examine daily patterns of allergic multimorbidity and work productivity in patients with allergic rhinitis. The mobile technology facilitates an innovative investigatory approach to better and more precisely characterize allergic multimorbidity. It provides novel insights in allergic multimorbidity. VAS global measured levels determine allergic multimorbidity. Four hypothesis-driven patterns were defined. In the population filling in the App (AR sufferers), there were hardly no Asthma High-Rhinitis Low or Conjunctivitis High-Rhinitis Low patterns. On the other hand, there were many days with Rhinitis High without asthma. The Asthma High-Rhinitis High and Conjunctivitis High-Rhinitis High (VAS global measured ≥ 50/100) was found in 2.9% days. It can be considered as the extreme uncontrolled

pattern. Work productivity was strongly correlated with VAS global measured levels, and also with the multimorbid patterns.

Strengths and limitations

There are potential measurement biases when using apps since the information collected is usually restricted and less complete than when using more detailled paper or web-based questionnaires. A bias might be introduced given that app users may be a selected subset and therefore not fully representative of all patients with rhinitis. Higher education or specific age ranges might apply. The study was not meant to be representative of the general population. The strengths and limitations of this study are those of mobile technology, as previously discussed [21,22]. Precise patient characterization is impossible using an App, but every observational study using the *Allergy Diary* was able to identify days with poor control or criteria of severity [19,21-23]. Mobile technology is likely to become an important tool to better understand and manage AR and asthma.

Smart devices and internet-based applications are already used in rhinitis but none have assessed allergic multimorbidity using days. This can be easily approached using the *Allergy Diary*. The strengths of the mobile technology include its wide acceptance and easy use, but there is a need to use appropriate questions, and results should be assessed by studies. This study was based on 4,210 users who filled in 32,585 days of VAS to answer some of the questions not yet studied [19,21-23].

Asthma was assessed using a single VAS largely validated in rhinitis [20]. In asthma, VAS was shown to be an effective measure of control [28]. In the present study, we did not investigate specific symptoms or perform any pulmonary function test. Thus, it is possible that some users may have misunderstood the question or overestimated the disease. However, the results are extremely consistent.

Stratification by age or sex has not been performed because in this study we considered days and not patients. This will be done at a later stage with a greater population.

We only considered days and not patients' trajectories because these are highly variable, patients using auto-medication depending on AR control (paper in preparation), and we need to develop a symptom-medication score (in preparation).

Generalizability

The results found a very low number of days of uncontrolled asthma or conjunctivitis without rhinitis. However, there may be a selection bias (users with AR using the App) and these results should be reproduced in a population in which asthma is the major claim.

The VAS nose has a major impact on the VAS global assessment of multimorbidities as it is more closely associated with it than VAS eyes or VAS asthma.

Asthma-rhinitis multimorbidity is well known [29] but the present study has added three novel findings: (i) Three uncontrolled patterns were found depending on VAS nose, eye and asthma. Rhinitis appears to be driving the overall loss of control of the disease but asthma and conjunctivitis are each adding some impact demonstrated by VAS global measured and VAS work. (ii) This study enabled a better appreciation of conjunctivitis multimorbidity. (iii) A novel extreme pattern of uncontrolled disease is associated with nose, eye and asthma multimorbidity. Interestingly, this extreme pattern was identified in MeDALL (Mechanisms of the Development of Allergy, FP7)[13,14] but not considered. In the hypothesis-driven analysis we combined rhinoconjunctivitis in the same multimorbidity analysis [14]. However, the data-driven cluster analysis showed that ocular symptoms were observed [15] confirming the results of the present study. New analyses will be done thanks to the results of the current study that stresses the importance of combining big data using undefined users and more classical epidemiological approaches. This phenotype was also identified in the EGEA study in which the prevalence of conjunctivitis is the highest in the asthma-rhinitis phenotype, but, again, not sufficiently considered.[28] These data strongly support the holistic and multidisciplinary approach of "one airway one disease" for the management of allergic airway diseases [29,30]. Although there is an increased number of days during the pollen season (March, April, May and June), there is a need to individually assess allergen exposure and pollution data to better understand the links between the nose, the eyes and the lower airways. This is the Horizon 2020 proposal POLLAR (Impact of air Pollution in asthma and rhinitis) recently funded.

Work impairment is confirmed in the present study. It extends the findings from our previous study with 5,600 days [21] as (i) the same levels of correlation between VAS work and VAS global measured, nose, eye or asthma were found in a larger population (17,505 days). (ii) According to correlations, the multimorbid pattern (VAS global measured) is the most closely associated with VAS work, followed by nose, eye and asthma. (iii) However, when comparing Rhinitis High phenotypic days, the levels of VAS work increased from a median of 37 (Asthma Low, Conjunctivitis Low), to 64 (Asthma High, Conjunctivitis High) showing the major impact of multimorbidity in work productivity. (iv) Finally, the study shows that, even in days with mild global symptoms, there is an impairment of work productivity confirming a recent study of the baseline characteristics of *Allergy Diary* using the Work-Productivity and Activity Questionnaire (WPAI-AS) [31].

The existence of different patterns of daily multimorbidity in people with rhinitis should be confirmed in a study combining individuals and days in the same analysis and using a cluster analysis and in general population and patient's cohorts with well-defined phenotypes. If confirmed, the results of the present study combined with other data generated by the *Allergy Diary* [19,21-23,31] will suggest to

propose "change management" [32] for rhinitis, asthma and conjunctivitis multimorbidity. For novel care pathways, we should consider both days and patients and not only patients. This approach would be helpful to patients as well as payers in concentrating resources on the most symptomatic days and where improvement would result in most effect personally and societal. The concept observed in this study may be expanded to other chronic diseases [31].

Conclusion

The present paper is a novel and intuitive way of presenting daily patterns of multimorbidity and stratifying risk of allergic rhinitis.

This analysis also suggests that big data that are soon coming to allergic diseases should be considered differently than the classical approach. They will complement our current knowledge, with the possibility of optimizing our practice of allergy.

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Table 1: Repartition of users

Country	Number of users	Country	Number of users
Austria	256	**Lithuania**	137
Australia	32	**Mexico**	197
Belgium	57	**Netherlands**	135
Brazil	205	**Poland**	230
Denmark	36	**Portugal**	866
Finland	225	**Spain**	258
France	420	**Sweden**	58
Germany	305	**Switzerland**	80
Greece	82	**UK**	117
Italy	500	**Others (not included)**	14

Table 2: Overall results

VAS Global	N (days)	Nose	Eye	Asthma	Work
0	7052	0 (0-0)	0 (0-0)	0 (0-1)	N=3260 0 (0-1)
1-9	6676	6 (3-10)	1 (0-6)	0 (0-4)	N=3820 2 (0-6)
10-19	5635	15 (10-20)	6 (0-15)	0 (2-20)	N=2623 10 (5-15)
20-29	3481	24 (18-31)	14 (0-25)	0 (2-20)	N=2001 18 (9-25)
30-39	2290	36 (26-42)	19 (1-35)	4 (0-28)	N=1219 24 (14-34)
40-49	1888	46 (36-53)	28 (6-47)	6 (0-33)	N=995 34 (20-45)
50-59	1682	53 (47-61)	39 (12-54)	10 (0-50)	N=966 44 (27-53)
60-69	1235	64 (54-71)	45 (16-65)	13 (0-54)	N=690 51 (36-61)
70-79	933	74 (62-80)	52 (21-74)	22 (0-26)	N=547 56 (39-68)
80-89	570	81 (71-87)	61 (23-83)	28 (0-78)	N=294 65 (47-77)
90-99	409	91 (79-96)	78 (45-94)	54 (5-92)	N=213 69 (52-85)
100	259	100 (86-100)	71 (28-100)	14 (0-68)	N=136 74 (59-99)

Table 3: VAS levels in days with severe rhinitis (VAS ≥ 50/100)

Nose Asthma Eye	High (≥50) Low (<20) Low (<20) A	High (≥50) Low <20) High (≥50) B	High (≥50) High (≥50) Low (<20) C	High (≥50) High (≥50) High (≥50) D	Significant data (Kruskal-Wallis, Bonferroni-Dunn)
N	1372 (4.2%)	1724 (5.3%)	520 (1.5%)	1039 (3.2%)	
VAS global	53 (44-67)	62 (51-75)	68 (55-82)	74 (59-88)	A/B, A/C, A/D, B/C, B/D, C/D
VAS nose	63 (54-77)	67 (57-79)	66 (58-78)	74 (61-88)	C/D
VAS eye	1 (0-9)	51 (35-68)	23 (6-37)	73 (59-85)	B/D (other comparisons not appriate)
VAS asthma	0 (0-2)	0 (0-5)	65 (56-77)	73 (60-86)	C/D (other comparisons not appriate)
VAS Work (N)	667	714	266	475	
VAS work	37 (16-53)	49 (30-61)	54 (36-51)	64 (53-77)	A/B, A/C, A/D, B/C, B/D, C/D

Results in medians and percentiles

Figure 1: Relationship between VAS Global and the other VAS scales (A) Percentage of days with VAS ≥1 and (B) median VAS levels in days with VAS ≥1

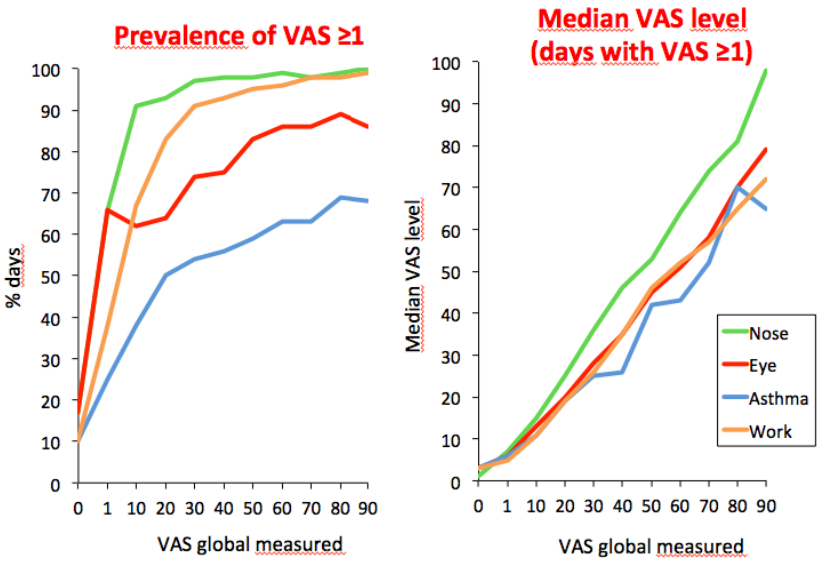


Figure 2: Correlation between VAS nose and VAS eye or asthma

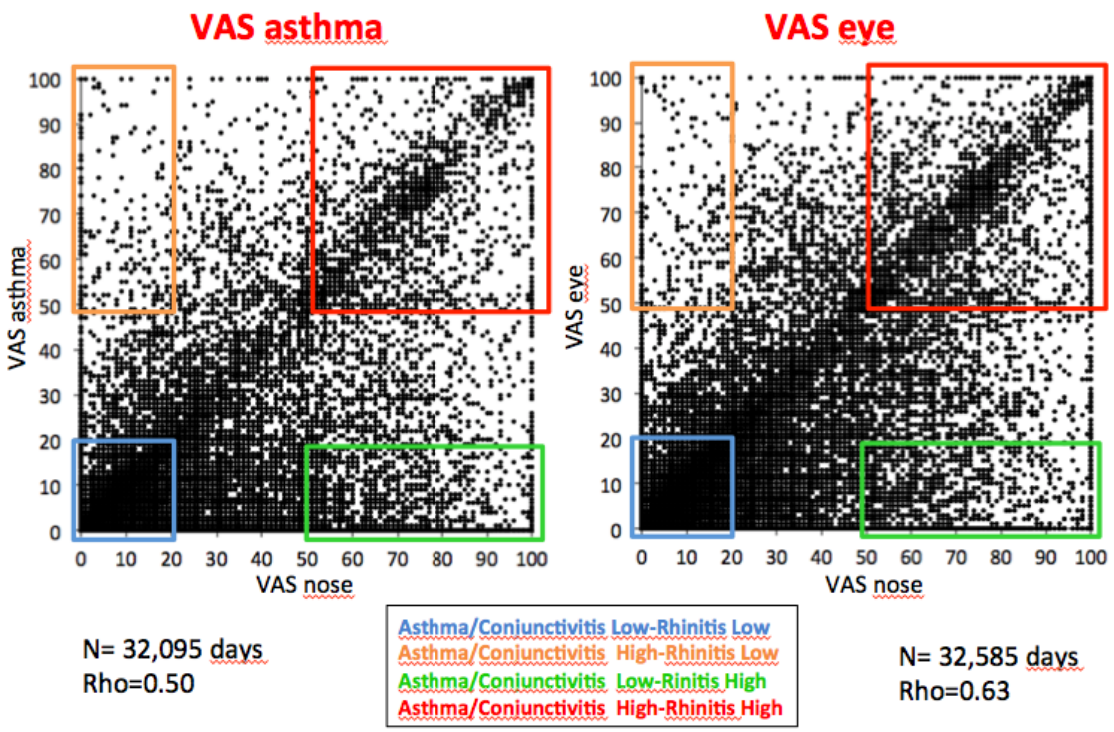
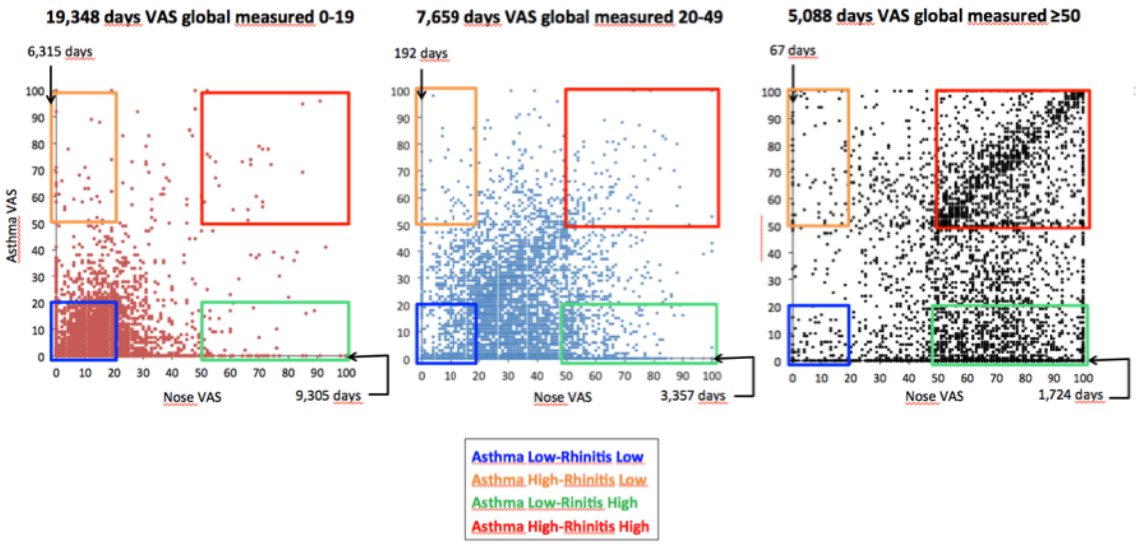


Figure 3: Daily asthma and rhinitis patterns



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